THE MEDICAL LETTER

a non-profit publication

on Drugs and Therapeutics

Published by Drug and Therapeutic Information, Inc., 136 East 57th Street, New York 22, New York

Vol. 3, No. 9 (Issue #60) April 28, 1961

COSA-TERRASTATIN, MYSTECLIN F AND DECLOSTATIN

The belief that the use of tetracycline antibiotics is likely to precipitate clinical infections by strains of Candida (Monilia) has led to the introduction of several new products containing combinations of a tetracycline with an antifungal agent. One of these, Cosa-Terrastatin (Pfizer), is similar to that company's earlier product, Cosa-Tetrastatin; nystatin is the antifungal agent in both, but oxytetracycline replaces tetracycline. A second combination, Mysteclin F (Squibb), combines tetracycline with a newer antifungal agent, amphotericin B (Fungizone - Squibb). A third product, Declostatin (Lederle), contains demethylchlortetracycline and nystatin.

The new products do not significantly change the view expressed in an early issue of The Medical Letter (1:15, 1959) that such combinations have very limited usefulness. Even though multiplication of Candida organisms may occur in the intestine during tetracycline therapy, clinically significant Candida infection of the intestinal or other mucosa seldom follows. Most gastrointestinal and other complications of tetracycline therapy are not of fungal origin; therefore, the addition of an antifungal agent to the antibiotic is not likely to provide effective prophylaxis against these complications.

INCREASE IN CANDIDA - The use of fungicides in combination with the tetracyclines apparently stems from the fact that an increased number of Candida organisms often appear in the stool following the use of a tetracycline, and that the number may be reduced by oral administration of nystatin or amphotericin B, both of which are effective against Candida species. Since many of the patients receiving tetracycline develop gastrointestinal symptoms, the coincidence of such symptoms and Candida multiplication in the stool is certain to occur. It cannot be assumed, however, that the overgrowth of Candida is responsible for the symptoms or that they would have been prevented if nystatin or amphotericin B had been used. Almost always, the Candida proliferation in the gastrointestinal tract is a transient, symptom-free condition requiring no treatment.

In double-blind studies, fungicides have seldom lessened the frequency or severity of gastrointestinal upsets associated with tetracycline therapy. Gastrointestinal side effects more often result from chemical irritation of the stomach or the intestines by the antibiotic or its break-down products, or from superinfection by tetracycline-resistant staphylococci.

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PROPHYLACTIC USES - Genital and anal itching sometimes follows tetracycline therapy, but the cause of such itching has not been determined. If anogenital itching tends to recur with tetracycline therapy, however, one of the combination antibiotics may be worth trying when tetracycline is again indicated, on the chance that Candida organisms are responsible for the itching.

Severe local or systemic Candida infections are most likely to occur in patients with marked impairment of natural defense mechanisms (such as those with lymphoma, leukemia, uncontrolled diabetes mellitus and hypogammaglobulinemia), in some infants, and in patients treated with nitrogen mustards and radiation, whether or not tetracycline has been used. When such patients need a tetracycline, the use of a combination containing an antifungal agent may be justified. Such infections are so infrequent, however, that a statistical study of their prevention by the combination of nystatin or amphotericin B with a tetracycline has been impossible.

TREATMENT - For the actual treatment of a Candida superinfection, whether it occurs spontaneously or as a complication of tetracycline therapy, full doses of a fungicide should be used and, most important, tetracycline therapy should be discontinued. For intestinal Candida superinfection, either nystatin or amphotericin B orally may be used. For systemic infection, only parenteral use of amphotericin B is likely to be effective (The Medical Letter, 1: 32, 1959).

One hazard in the routine use of tetracycline-fungicide combinations is that inhibition or eradication of the fungus might favor overgrowth of potentially more dangerous organisms. In one study with tetracycline-nystatin, nystatin did, in fact, appear to favor the growth of Pseudomonas (M. H. Lepper and J. Z. Pearson, Antibiotics Annual, 1956-1957, p. 221).

HAZARD OF RESISTANT STRAINS - A more serious possibility is that widespread use of the antifungal agents would favor propagation of resistant strains of fungi. In one in vitro study with a single strain of Candida albicans, no increase in resistance to nystatin or amphotericin B developed, but other Candida species developed resistance to both agents. Cross-resistance between nystatin and amphotericin B was also demonstrated (M. L. Littman, et al., Antibiotics Annual, 1957-1958, p. 981).

Since the difference between the maximum achievable blood levels of the drug and the inhibitory concentration for most pathogenic fungi is small, minor increases in resistance to amphotericin B could render this drug clinically ineffective. One cannot rule out the possibility that the routine use of nystatin and amphotericin B in combination with broad-spectrum antibiotics as prophylaxis against Candida infection could lead to the increased resistance of many pathogenic fungi to both agents. Such an effect could be disastrous for patients with disseminated mycoses, for which amphotericin B is the only effective medication now available.

Medical Letter consultants believe that the routine prophylactic use of antifungal agents along with tetracyclines cannot be justified. When an antifungal agent is needed, it is best to use either nystatin or amphotericin B in full therapeutic doses.

TIMOVAN

Prothipendyl hydrochloride (Timovan - Ayerst) is described by the manufacturer as a completely new "calmative...designed specifically for active patients in need of calming without the 'slow-down' of sedatives or the hazards of many tranquilizers." Chemically, Timovan is a thiophenylpyridylamine derivative closely related to the phenothiazines; it differs from chlorpromazine (Thorazine - SKF) in the substitution of a pyridine ring for the chlorinated benzene ring.

FOREIGN STUDIES - Very few studies of the drug are available. The manufacturer cites two German studies on the tranquilizing effects of Timovan, one from the Medical Clinic of the Medical Academy of Magdeburg and one from the Psychiatric Department of the University of Halle. The Magdeburg paper, based on an extensive and detailed clinical-pharmacologic survey, indicates that the compound is much like chlorpromazine in its action. The author notes his impression that Timovan had somewhat less sedative effect orally than Thorazine, though he found very little difference when the drugs were administered parenterally. Timovan appeared to have greater antihistaminic effect than Thorazine. When given parenterally, it caused marked hypotension.

No toxic effects are reported in either of the German studies. Since reports of toxic and side reactions are often slow to appear, the manufacturer's claim that Timovan is "remarkably free of side effects" seems premature. Neither report contains evidence of a controlled or comparative study with the phenothiazines. Unless details of adequately controlled double-blind studies are included in reports on new psychopharmacologic agents, claims as to the effects of such agents can be little more than unconfirmed surmise.

It can be said at this point only that an agent has been developed which is chemically related to chlorpromazine. The scant pharmacologic and clinical evidence seems to indicate that the new drug is similar to chlorpromazine in its actions. Supposed differences in its activity require scientific proof, and the claims made for Timovan are not so far supported by adequate studies.

MORE ORAL THIAZIDE DIURETICS

Benzthiazide (NaClex - Robins) and methyclothiazide (Enduron - Abbott) are two new oral thiazides which appear to be as effective in producing diuresis as the older compounds in this group of sulfonamide diuretics.

NACLEX - One reference given by the manufacturer indicates that NaClex is equivalent to hydrochlorothiazide (Hydrodiuril - Merck; Esidrix - Ciba; Oretic - Abbott) in almost all essential respects, including milligram dosage (R. V. Ford, Current Ther. Res., 2:51, 1960).

Among the side effects of NaClex reported in the company brochure are nausea, anorexia and headache, and rare instances of hyperuricemia, leukopenia and rash. Side effects which occur occasionally with the sulfonamide diuretics also include other gastrointestinal complaints, jaundice, increased hepatic de-

compensation in hepatic cirrhosis, photosensitization, and rarely, other blood dyscrasias, acute glomerulonephritis, and pancreatitis. With all of these diuretics, the physician must be on guard against excessive potassium depletion which may, among other effects, cause muscle weakness and precipitate digitalis intoxication. These drugs may also aggravate diabetes and gout; and they may decrease responsiveness to norepinephrine or augment the paralyzing effect of tubocurarine.

ENDURON - The promotion for Enduron claims more prolonged action, greater milligram potency, greater peak-dosage effectiveness, and less potassium loss than with any other thiazide. A promotion letter states that "Enduron's dosage has been engineered for the most practical schedule there is: once a day, every day." The "most practical schedule" of thiazide prescription varies from patient to patient, however, and from time to time with the same patient. The schedule is affected by individual responsiveness, rate of reaccumulation of fluid, associated metabolic state, and concurrent use of other drugs, such as digitalis and corticosteroids. Moreover, it is often desirable to use thiazides intermittently rather than every day, to permit replenishment of potassium and excretion of retained uric acid.

Each of several thiazide diuretics is claimed to cause less potassium loss than the others. With none, however, have the differences been shown to be clinically significant. Loss of potassium in clinical practice depends more on such factors as sodium intake, resistance to sodium diuresis because of aldosterone excess (for example, in edema associated with nephrosis or liver cirrhosis), anorexia, vomiting or diarrhea than on the diuretic chosen (The Medical Letter, 2:57, 1960). The same side effects must be expected with Enduron as with the other drugs in this group.

Eight oral thiazide diuretics (and Hygroton — a non-thiazide sulfonamide with similar diuretic properties) are now available. It is possible that longer experience will show important advantages for one or another of these drugs, but there now appears to be no advantage either in effectiveness or in incidence of side effects which would make any of the newer ones superior to Chlorothiazide, USP (Diuril - Merck), the thiazide which has had the longest use. Increased milligram potency offers neither greater effectiveness nor greater freedom from side effects or hypersensitivity reactions. If any one of these drugs gives inadequate diuresis, a different one is not likely to be more effective.

In the most resistant instances of congestive heart failure, the sulfonamide diuretic may have to be combined with mercurial agents, spironolactone (Aldactone - Searle), adrenal corticosteroids, or a combination of these agents.

COLCHICINE DOSAGE - CORRECTION

An error of transcription in an appraisal of uricosuric drugs (The Medical Letter, 3:11, Feb. 3, 1961) resulted in incorrect dosage figures for colchicine for prophylaxis against acute attacks of gout. The correct dosage is one 0.5-mg. tablet one to three times a day. (NOTE: The correct dosage is given in reprints of the Feb. 3, 1961 issue.)

THE MEDICAL LETTER ON DRUGS AND THERAPEUTICS is published fortnightly by Drug and Therapeutic Information, a non-profit corporation, 136 E. 57th St., New York 22, N. Y. Second-class postage paid at New York, N. Y. Subscription fees: 1 yr., $12.50; 2 yrs., $23; 3 yrs., $34 ($6.25 per year for residents, interns, students).